

Notice of Allowability

Application No.

10/719,480

Applicant(s)

ZHANG ET AL.

Examiner

Frank W. Lu

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 5/22/2007 and 7/31/2007.
2. ☒ The allowed claim(s) is/are 1,2,23,24,33 and 34.
3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some* c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
- (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
- 1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
- (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
- Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date 7/27/2007
4. ☐ Examiner's Comment Regarding Requirement for Deposit
of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413),
Paper No./Mail Date _____.
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

DETAILED ACTION

Reasons for Allowance

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Dr. Amy Wilson (Reg. No. 54,704) on October 15 2007.

2. The application has been amended as follows:

Cancel claims 3, 4, 8, 9, 13, 14, 18, 19, 28, 29, 38, 39, and 43-45.

1. (currently amended) A method for detecting a target nucleic acid in a nucleic acid containing sample comprising:

(a) contacting the [target] nucleic acid containing sample with a circular oligonucleotide probe under conditions that allow hybridization between complementary sequences in the target nucleic acid and the circular oligonucleotide probe;

(b) adding at least one forward primer comprising a sequence complementary to a portion of the circular oligonucleotide probe, under conditions where the forward primer is extended around the circular oligonucleotide probe for multiple revolutions to form a single-stranded DNA molecule [of] comprising repeating units complementary to the sequence of the circular probe;

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(c) adding at least one oligonucleotide primer pair comprising a first primer and a second primer, wherein

(i) the first primer of the pair comprises (A) a first sequence on its 3' end that is substantially identical to a portion of the circular oligonucleotide probe, (B) a second sequence that is complementary to the second primer of the pair, and (C) a signal generating moiety selected from the group consisting of a fluorescent agent and a chemiluminescent agent;

(ii) the second primer of the pair comprises (A) a sequence that is complementary to the first primer and (B) a moiety capable of quenching, masking or inhibiting the activity of the signal generating moiety when located adjacent to, or in close proximity to the signal generating moiety; and

(iii) when the first primer and the second primer are bound to one another, [the signal] a signal generated by the signal generating moiety is inhibited;

(d) adding at least one reverse primer comprising a sequence that is substantially identical to a portion of the circular oligonucleotide probe and wherein the forward primer, reverse primer, and the first primer and the second primer of the oligonucleotide primer pair are not identical;

(e) adding a DNA polymerase having strand displacement activity and lacking 3' to 5' exonuclease activity; and

(f) amplifying the circular oligonucleotide probe using ramification-extension amplification method (RAM) thus producing an amplification product comprising a sequence that is substantially identical to a sequence in the circular probe, and separating the signal generating moiety selected from the group consisting of a fluorescent agent and a

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chemiluminescent agent [and] from the quenching, masking or inhibitory moiety [to generate a signal] by the action of the DNA polymerase having strand displacement activity and lacking 3' to 5' exonuclease activity during the amplification method, wherein detection of the signal indicates the presence of the target nucleic acid in the nucleic acid containing sample.

2. (Currently amended) A method for detecting a target nucleic acid in a nucleic acid containing sample comprising:

(a) contacting the nucleic acid containing sample with a linear oligonucleotide probe comprising 3' and 5' regions complementary to adjacent sequences in the target nucleic acid under conditions that allow hybridization between complementary sequences in the target nucleic acid and the linear oligonucleotide probe, whereupon binding to the target nucleic acid, the 3' and 5' ends of the linear oligonucleotide probe are adjacent to each other such that ligation of the 3' and 5' ends of the linear oligonucleotide probe forms the circular oligonucleotide probe, ligating the 3' and 5' ends of the linear oligonucleotide probe, and forming a circular oligonucleotide probe when the target nucleic acid is in the nucleic acid containing sample;

(b) adding at least one forward primer comprising a sequence complementary to a portion of the circular oligonucleotide probe, under conditions where the forward primer is extended around the circular oligonucleotide probe for multiple revolutions to form a single-stranded DNA molecule comprising repeating units complementary to the sequence of the circular probe;

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(c) adding at least one oligonucleotide primer pair comprising a first primer and a second primer, wherein

(i) the first primer of the pair comprises (A) a first sequence on its 3' end that is substantially identical to a portion of the circular oligonucleotide probe, (B) a second sequence that is complementary to the second primer of the pair, and (C) a signal generating moiety selected from the group consisting of a fluorescent agent and a chemiluminescent agent;

(ii) the second primer of the pair comprises (A) a sequence that is complementary to the first primer and (B) a moiety capable of quenching, masking or inhibiting the activity of the signal generating moiety when located adjacent to, or in close proximity to the signal generating moiety; and

(iii) when the first primer and the second primer are bound to one another, a signal generated by the signal generating moiety is inhibited;

(d) adding at least one reverse primer comprising a sequence that is substantially identical to a portion of the circular oligonucleotide probe and wherein the forward primer, reverse primer, and the first primer and the second primer of the oligonucleotide primer pair are not identical;

(e) adding a DNA polymerase having strand displacement activity and lacking 3' to 5' exonuclease activity; and

(f) amplifying the circular oligonucleotide probe using ramification-extension amplification method (RAM) thus producing an amplification product comprising a sequence that is substantially identical to a sequence in the circular probe, and separating the signal generating moiety selected from the group consisting of a fluorescent agent and a

chemiluminescent agent from the quenching, masking or inhibitory moiety by the action of the DNA polymerase having strand displacement activity and lacking 3' to 5' exonuclease activity during the amplification method, wherein detection of the signal indicates the presence of the target nucleic acid in the nucleic acid containing sample [The method of claim 1, whereby the circular oligonucleotide probe is formed by ligating the 3' and 5' ends of a linear oligonucleotide probe, comprising 3' and 5' regions complementary to adjacent sequences in the target nucleic acid under conditions that allow hybridization between complementary sequences in the target nucleic acid and the linear oligonucleotide probe, whereupon binding to the target nucleic acid, the 3' and 5' ends of the linear oligonucleotide probe are adjacent to each other such that ligation of the 3' and 5' ends of the linear oligonucleotide probe form the circular oligonucleotide probe].

23. (currently amended) A method for detecting a target nucleic acid in a nucleic acid containing sample comprising:

- (a) contacting the [target] nucleic acid containing sample with a circular oligonucleotide probe under conditions that allow hybridization between complementary sequences in the target nucleic acid and the circular oligonucleotide probe;
- (b) adding at least one multiple oligonucleotide primer complex comprising a first primer, a second primer and a third primer, under conditions where the multiple oligonucleotide primer complex is extended around the circular oligonucleotide probe for multiple revolutions to form a single-stranded DNA molecule [of] comprising repeating units complementary to the sequence of the circular oligonucleotide probe, wherein

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- (i) the first primer of the multiple oligonucleotide primer complex comprises (A) a first sequence on its 3' end that is complementary to a portion of the circular oligonucleotide probe, (B) a second sequence that is complementary to the second primer of the multiple oligonucleotide primer complex, and (C) a third sequence that is complementary to the third primer of the multiple oligonucleotide primer complex;
- (ii) the second primer of the multiple oligonucleotide primer complex comprises (A) a sequence that is complementary to the second sequence of the first primer of the multiple oligonucleotide primer complex and (B) a signal generating moiety selected from the group consisting of a fluorescent agent and a chemiluminescent agent;
- (iii) the third primer of the multiple oligonucleotide primer complex comprises (A) a sequence that is complementary to the third sequence of the first primer of the multiple oligonucleotide primer complex and (b) a moiety capable of quenching, masking or inhibiting the activity of the signal generating moiety when located adjacent to, or in close proximity to the signal generating moiety; and
- (iv) when the first, second and third primers of the multiple oligonucleotide primer complex are bound to one another, [the signal] a signal generated by the signal generating moiety is inhibited;
- (c) adding at least one reverse primer comprising a sequence that is substantially identical to a portion of the circular oligonucleotide probe;
- (d) adding a DNA polymerase having strand displacement activity and lacking 3' to 5' exonuclease activity; and

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(e) amplifying the circular oligonucleotide probe using ramification-extension amplification method (RAM) thus producing an amplification product comprising a sequence that is substantially identical to a sequence in the circular oligonucleotide probe, and separating the signal generating moiety [and] from the quenching, masking or inhibitory moiety to generate a signal by the action of the DNA polymerase having strand displacement activity and lacking 3' to 5' exonuclease activity during the amplification method, wherein detection of the signal indicates the presence of the target nucleic acid in the nucleic acid containing sample.

24. (Currently amended) A method for detecting a target nucleic acid in a nucleic acid containing sample comprising:

(a) contacting the nucleic acid containing sample with a linear oligonucleotide probe comprising 3' and 5' regions complementary to adjacent sequences in the target nucleic acid under conditions that allow hybridization between complementary sequences in the target nucleic acid and the linear oligonucleotide probe, whereupon binding to the target nucleic acid, the 3' and 5' ends of the linear oligonucleotide probe are adjacent to each other such that ligation of the 3' and 5' ends of the linear oligonucleotide probe form the circular oligonucleotide probe, ligating the 3' and 5' ends of a linear oligonucleotide probe, and forming a circular oligonucleotide probe when the target nucleic acid is in the nucleic acid containing sample;

(b) adding at least one multiple oligonucleotide primer complex comprising a first primer, a second primer and a third primer, under conditions where the multiple

oligonucleotide primer complex is extended around the circular oligonucleotide probe for multiple revolutions to form a single-stranded DNA molecule comprising repeating units complementary to the sequence of the circular oligonucleotide probe, wherein

(i) the first primer of the multiple oligonucleotide primer complex comprises (A) a first sequence on its 3' end that is complementary to a portion of the circular oligonucleotide probe, (B) a second sequence that is complementary to the second primer of the multiple oligonucleotide primer complex, and (C) a third sequence that is complementary to the third primer of the multiple oligonucleotide primer complex;

(ii) the second primer of the multiple oligonucleotide primer complex comprises (A) a sequence that is complementary to the second sequence of the first primer of the multiple oligonucleotide primer complex and (B) a signal generating moiety selected from the group consisting of a fluorescent agent and a chemiluminescent agent;

(iii) the third primer of the multiple oligonucleotide primer complex comprises (A) a sequence that is complementary to the third sequence of the first primer of the multiple oligonucleotide primer complex and (b) a moiety capable of quenching, masking or inhibiting the activity of the signal generating moiety when located adjacent to, or in close proximity to the signal generating moiety; and

(iv) when the first, second and third primers of the multiple oligonucleotide primer complex are bound to one another, a signal generated by the signal generating moiety is inhibited;

(c) adding at least one reverse primer comprising a sequence that is substantially identical to a portion of the circular oligonucleotide probe;

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(d) adding a DNA polymerase having strand displacement activity and lacking 3' to 5' exonuclease activity; and

(e) amplifying the circular oligonucleotide probe using ramification-extension amplification method (RAM) thus producing an amplification product comprising a sequence that is substantially identical to a sequence in the circular oligonucleotide probe, and separating the signal generating moiety from the quenching, masking or inhibitory moiety to generate a signal by the action of the DNA polymerase having strand displacement activity and lacking 3' to 5' exonuclease activity during the amplification method, wherein detection of the signal indicates the presence of the target nucleic acid in the nucleic acid containing sample [The method of claim 23, whereby the circular oligonucleotide probe is formed by ligating the 3' and 5' ends of a linear oligonucleotide probe, comprising 3' and 5' regions complementary to adjacent sequences in the target nucleic acid under conditions that allow hybridization between complementary sequences in the target nucleic acid and the linear oligonucleotide probe, whereupon binding to the target nucleic acid, the 3' and 5' ends of the linear oligonucleotide probe are adjacent to each other such that ligation of the 3' and 5' ends of the linear oligonucleotide probe form the circular oligonucleotide probe].

33. (Currently amended) A method for detecting a target nucleic acid in a nucleic acid containing sample comprising:

(a) contacting the [target] nucleic acid containing sample with a circular oligonucleotide probe under conditions that allow hybridization between complementary sequences in the target nucleic acid and the circular oligonucleotide probe;

(b) adding at least one forward primer comprising a sequence that is complementary to a portion of the circular oligonucleotide probe, under conditions where the forward primer is extended around the circular oligonucleotide probe for multiple revolutions to form a single-stranded DNA molecule [of] comprising repeating units complementary to the sequence of the circular oligonucleotide probe;

(c) adding at least one multiple oligonucleotide primer complex comprising a first primer, a second primer and a third primer, wherein

(i) the first primer of the multiple oligonucleotide primer complex comprises (A) a first sequence on its 3' end that is substantially identical to a portion of the circular oligonucleotide probe, (B) a second sequence that is complementary to the second primer of the pair, and (C) a third sequence that is complementary to the third primer of the multiple oligonucleotide primer complex;

(ii) the second primer of the multiple oligonucleotide primer complex comprises (A) a sequence that is complementary to the second sequence of the first primer of the multiple oligonucleotide primer complex and (B) a signal generating moiety selected from the group consisting of a fluorescent agent and a chemiluminescent agent;

(iii) the third primer of the multiple oligonucleotide primer complex comprises (A) a sequence that is complementary to the third sequence of the first primer of the multiple oligonucleotide primer complex and (b) a moiety capable of quenching, masking or inhibiting the activity of the signal generating moiety when located adjacent to, or in close proximity to the signal generating moiety; and

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(iv) when the first, second and third primers of the multiple oligonucleotide primer complex are bound to one another, [the signal] a signal generated by the signal generating moiety is inhibited; and

(d) adding a DNA polymerase having strand displacement activity and lacking 3' to 5' exonuclease activity; and

(e) amplifying the circular oligonucleotide probe using ramification-extension amplification method (RAM) thus producing an amplification product comprising a sequence that is substantially identical to a sequence in the circular oligonucleotide probe, and separating the signal generating moiety [and] from the quenching, masking or inhibitory moiety to generate a signal by the action of the DNA polymerase having strand displacement activity and lacking 3' to 5' exonuclease activity during the amplification method, wherein detection of the signal indicates the presence of the target nucleic acid in the nucleic acid containing sample.

34. (Currently amended) A method for detecting a target nucleic acid in a nucleic acid containing sample comprising:

(a) contacting the nucleic acid containing sample with a linear oligonucleotide probe comprising 3' and 5' regions complementary to adjacent sequences in the target nucleic acid under conditions that allow hybridization between complementary sequences in the target nucleic acid and the linear oligonucleotide probe, whereupon binding to the target nucleic acid, the 3' and 5' ends of the linear oligonucleotide probe are adjacent to each other such that ligation of the 3' and 5' ends of the linear oligonucleotide probe forms the circular oligonucleotide probe, ligating the 3' and 5' ends of the linear oligonucleotide probe, and

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forming a circular oligonucleotide probe when the target nucleic acid is in the nucleic acid containing sample;

(b) adding at least one forward primer comprising a sequence that is complementary to a portion of the circular oligonucleotide probe, under conditions where the forward primer is extended around the circular oligonucleotide probe for multiple revolutions to form a single-stranded DNA molecule comprising repeating units complementary to the sequence of the circular oligonucleotide probe;

(c) adding at least one multiple oligonucleotide primer complex comprising a first primer, a second primer and a third primer, wherein

(i) the first primer of the multiple oligonucleotide primer complex comprises (A) a first sequence on its 3' end that is substantially identical to a portion of the circular oligonucleotide probe, (B) a second sequence that is complementary to the second primer of the pair, and (C) a third sequence that is complementary to the third primer of the multiple oligonucleotide primer complex;

(ii) the second primer of the multiple oligonucleotide primer complex comprises (A) a sequence that is complementary to the second sequence of the first primer of the multiple oligonucleotide primer complex and (B) a signal generating moiety selected from the group consisting of a fluorescent agent and a chemiluminescent agent;

(iii) the third primer of the multiple oligonucleotide primer complex comprises (A) a sequence that is complementary to the third sequence of the first primer of the multiple oligonucleotide primer complex and (b) a moiety capable of quenching, masking or

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inhibiting the activity of the signal generating moiety when located adjacent to, or in close proximity to the signal generating moiety; and

(iv) when the first, second and third primers of the multiple oligonucleotide primer complex are bound to one another, a signal generated by the signal generating moiety is inhibited; and

(d) adding a DNA polymerase having strand displacement activity and lacking 3' to 5' exonuclease activity; and

(e) amplifying the circular oligonucleotide probe using ramification-extension amplification method (RAM) thus producing an amplification product comprising a sequence that is substantially identical to a sequence in the circular oligonucleotide probe, and separating the signal generating moiety from the quenching, masking or inhibitory moiety to generate a signal by the action of the DNA polymerase having strand displacement activity and lacking 3' to 5' exonuclease activity during the amplification method, wherein detection of the signal indicates the presence of the target nucleic acid in the nucleic acid containing sample [The method of claim 33, whereby the circular oligonucleotide probe is formed by ligating the 3' and 5' ends of a linear oligonucleotide probe, comprising 3' and 5' regions complementary to adjacent sequences in the target nucleic acid under conditions that allow hybridization between complementary sequences in the target nucleic acid and the linear oligonucleotide probe, whereupon binding to the target nucleic acid, the 3' and 5' ends of the linear oligonucleotide probe are adjacent to each other such that ligation of the 3' and 5' ends of the linear oligonucleotide probe form the circular oligonucleotide probe].

3. The following is an examiner's statement of reasons for allowance:

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Claims 1, 2, 23, 24, 33, and 34 are allowable in light of applicant's amendments filed on May 22, 2007 and July 31, 2007 and the examiner's amendments. The rejections under 35 U.S.C 112, first paragraph and second paragraph have been withdrawn in view of the applicant's amendments filed on May 22, 2007 and July 31, 2007 and the examiner's amendments. The support for the amendments is from Figure 32, page 50, [00172] and pages 54 and 55, [00183] and [00184] of the specification. The closest prior art in the record are Zhang *et al.*, (US Patent No. 5,942,391, published on August 24, 1999), Wang *et al.*, (US Patent NO. 5,567,583, published on October 22, 1996), Harris (US Patent No. 5,837,469, published on November 17, 1998), and Coull *et al.*, (WO 99/49293, published on September 30, 1999). These prior art in the record do not teach steps b) to (f) of claims 1 and 2 and steps b) to (e) of claims 23, 24, 33, and 34. The prior art in the record does not teach or reasonably suggest a method for detecting a target nucleic acid in a nucleic acid containing sample which comprises all of the limitations recited in claims 1, 2, 23, 24, 33, and 34.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Drawings

4. Newly submitted Figure 18 has been accepted by the office.
5. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30

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(November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746.

The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

October 15, 2007


FRANK LU
PRIMARY EXAMINER